**Cooper Presents:** 

# City Wide Conference 11/27/18

Shares in faces if it. 75 first second law Sec.

# Citywide Conference Case 1 11/27/18

• Cooper

University Hospital

Aleksandr Yakubov DO

PGY-4



Cooper Medical School of Rowan University

#### Case 1

#### ► 45 y.o. Caucasian female

#### Presents from outside hospital with progressive bilateral upper extremity weakness

#### Case 1

- Presented on 9/24/18 to OSH with neck pain, tremors, tingling, and numbress in hands
  - symptom onset 3-5 days prior
  - Workup in ED included CT head with no abnormalities
  - Discharged home the same day
- Neck pain continued 4 hours post-discharge
  - developed fevers, whole body tremors, and
  - RUE weakness("could not hold a mug"), weaker in right shoulder, progressed to right hand, with inability to move fingers
- Has been well otherwise with no recent hospitalizations or illnesses

#### Case 1:

- Additional workup included:
  - MRI brain did not reveal any abnormalities
  - MRI spine w/ and w/o showing "elongated right cord lesion from C3-C6 suggesting inflammation consistent with transverse myelitis" with no enhancement of the cord
- LP at OSH showing
  - ▶ WBC 300 (40% neutrophils, 34% lymphocytes, 8% monocytes)
  - Protein 89
  - ► Glucose 60
  - RBCs 17
- Started on IV acyclovir and methylprednisolone
   Transferred on 09/26 to CUH (Hospital Day 3)

#### Additional History obtained since transfer

- Lives in Juniper, Florida most of the year
- Works in Cape May, NJ for the summer; works in Real Estate
- No travel outside of the country
- No pets
- ▶ No tobacco, alcohol, or drug use
- Denies hiking recently or in the past; spends a lot of time on the beach

#### Pertinent ROS

- Constitutional: + fever, chills and weakness
  - Negative for weight loss/gain
- MSK: + neck pain and stiff neck. Negative for swelling.
- Skin: Negative for rash
- Neurological: + tingling, tremors, sensory change and focal weakness
  - Negative for dizziness, vertigo, seizures and loss of balance.

#### Pertinent Physical Exam

Vitals

- ▶ BP 101/62 HR 98 RR 26, Sp02-95% T 100.8
- Constitutional: well-developed and well-nourished. No acute distress.
- CV, Pulmonary, Abdominal Exam WNL, no LAD
- Musculoskeletal: Normal mm bulk, low tone b/l upper extremities.
- Neuro: AAO x 3, cranial nerves intact Strength: LUE: Proximal 2/5 and Distal 5/5 RUE: Proximal 1/5 and Distal 3/5,
- Moves fingers in plane of gravity but no grip strength B/l LE: 5/5
- Reflexes: RUE 1+ RLE 1+ LUE 2+ LLE 2+

Sensory: Intact sensation to light touch, vibration and pinprick



#### Lab studies



- 96.4% neutrophils
- 2.7% lymphocytes
- 0.9% monocytes
  - PT 10.4
  - INR 0.9
  - PTT 24.1

- AST 16
- ▶ ALT 16
- ALK PHOS 38
- ▶ T-BILI 0.4
- PROTEIN 6.7

► TSH 0.3

- ► ESR 4
- CRP 0.06

#### MRI brain



Few T2/FLAIR hyperintense foci within the subcortical and deep white matter are a nonspecific finding and may be seen with demyelination

#### 9/27 MRI Spine

Extensive abnormal signal intensity within the central portion of the cervical cord affecting the central gray matter tracts with subtle regions of patchy enhancement. The overall appearance is most suggestive of changes of transverse myelitis. Normal appearance of the thoracic cord and conus. No evidence of cord compressing lesion throughout the spinal axis

There is **segmental abnormal increased signal intensity** on T2, STIR and gradient echo imaging within central portions of the cervical cord involving central gray matter structures. This is seen **throughout the entire cervical cord down to the level of C7-T1**. There also appears to be **patchy enhancement** following contrast administration



#### **Differential Diagnosis?**

45 y/o woman presenting with acute onset UE >> LE weakness, fevers, and neck pain, with spinal imaging consistent with transverse myelitis and abnormal LP

### Additional Workup at CUH:

- Neurology and ID evaluation early on for possible noninflammatory vs infectious conditions that may mimic transverse myelitis including:
  - Metabolic and nutritional myelopathies
  - Neoplasms, paraneoplastic syndrome
  - Radiation myelitis
  - Infections: (ie enterovirus, WNV, herpes, CNS Lyme disease, mycoplasma)
  - Systemic rheumatologic disease (ie SLE, Sjögren
  - Multifocal neurologic disease (ie MS, neuromyelitis optica, acute disseminated encephalomyelitis)
- Started on doxycycline and ceftriaxone, continued solumedrol and IV acyclovir

### Clinical Course at CUH:

- Over first few days weakness worsened with concern for diaphragmatic involvement
- Initially noted to be hypophonetic
- Remained alert and oriented x3 throughout the hospitalization
- Minor improvement in motor strength, reflexes, and speech over a few day period
  - Waxing and waning motor strength in the initial days of hospitalization
- Heme/onc later consulted for possible plasmapheresis

#### Additional tests

- Lab tests from outside hospital as well as tests sent from CUH
  - Serum Cryptococcus Ag negative
  - Serum Lyme-Ab negative
  - Serum VDRL-negative
  - Serum IgG-negative(800)
  - ▶ HIV 1/2 Ab neg , p24 Ag negative, VL negative
  - Serum CMV PCR neg
  - Serum HSV 1/2 Ab neg
  - RPR neg
  - Homocysteine, b12, copper WNL
  - Serum EBV-IgG reactive(capcid, nuclear AG), negative capsid IgM
  - Serum West Nile IgG negative
  - Serum West Nile IgM equivocal
  - CSF cultures-few polys, no growth

## Additional work-up: 2<sup>nd</sup> LP

	10/2	9/24
WBC	35	300
Differential		
Neutrophils	0%	40%
Lymphocytes	<b>95</b> %	34%
Monocytes	5%	8%
RBCs	17	17
Protein	80	89
Glucose	54	60

Started apheresis on 10/3 to 10/6

#### **Differential Diagnosis?**

45 y/o woman presenting with acute onset UE >> LE weakness, fevers, and neck pain, with spinal imaging consistent with transverse myelitis, with minimal clinical improvement and CSF profile evolving to lymphocyte predominance over 1 week, and no diagnostic serologies thus far

#### **OSH results**

- 10/5 called from OSH stating that IgM from CSF was positive for West Nile
- All antimicrobials stopped
- Patient continued to slowly regain strength, improved speech

 West Nile Virus Ab, IgG, CSF
 SUL

 West Nile Virus Ab, IgG, CSF
 SUL

 Negative
 Negative

 West Nile Virus Ab, IgM, CSF
 SUL

 Positive
 Negative

West Nile CSF Interpretation

Abn

① SDL

#### Discussion

#### West Nile Virus

- first isolated from a febrile woman in the West Nile region of Uganda, Africa in 1937
- since the New York City outbreak in 1996, severe neurological illness, including encephalitis and meningitis, has been reported much more frequently, together with neuromuscular manifestations
- 59 human cases reported from 20 NJ counties, including 3 fatalities in Bergen County (NJ Dept of Health)
  - ▶ Vs 102 in PA, and 79 in NY thus far
  - Highest number of cases ever reported in NJ
  - 42 cases classified with neuroinvasive disease

#### Acute transverse myelitis

- estimated incidence of 1.34 to 4.6 per million
- reported to be as high as 3.1 per 100,000 patient years (West 2013)

Mosquito-borne diseases			
	2018 <sup>b</sup>	2017	
Chikungunya	9	12	
Dengue	16	25	
Eastern equine encephalitis	-	-	
Malaria	79	125	
West Nile	59	8	
Zika	7	37	



2018 West Nile Total cases disease cases more than 16,000 cases of WNV neuroinvasive disease reported across the USA since 1999

#### 2018 West Nile Neuroinvasive disease incidence



#### West Nile Recovery

- Recovery from neurological sequelae of WNV neuroinvasive disease may be slow and incomplete (Davis, <u>2006</u>), with a poorer prognosis for recovery of physical function in patients with acute flaccid paralysis (Johnstone, <u>2011</u>)
  - According to some case series: 1/3 recover strength to near baseline, 1/3 modestly improve, 1/3 fail to improve
  - Recover mostly within first 6-8 months
  - If quadriplegia and respiratory failure, associated with high M&M
  - However, even patients with initially severe and profound paralysis may experience profound recovery

# Myelopathy in West Nile virus encephalitis: Report of a case and review of literature

Jayantee Kalita 🚬, Amar Vibhute, Mritunjai Kumar & Usha K. Misra Published online: 20 Aug 2018

EMG may be helpful in confirming anterior horn cell involvement and predicting outcome

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## **Additional Questions**





#### Case 2: 3 Year Old Male With Fever and Headache

- Unvaccinated male with no sig PMHx
- 2 day PTA onset of fever to 101 with nasal congestion, cough, HA and fatigue.
- Persistent HA, decreased appetite and fever and brought to OSH, and admitted to r/o serious bacterial infection.
- Parents describe child as being sleepier than usual and "not able to hold his head up." and complaining of neck pain
- Non bloody or bilious emesis and continued HA despite IVF hydration, NSAIDS and empiric antibiotics: vancomycin and ceftriaxone

#### 3 Year Old Male With Fever and Headache

- Initial valuation at outside hospital:
- TMax 38.5° C, remainder of VS normal
- CBC: 16.4 N 72% L 22% M 6% Hgb 11.2 Plt 465K CRP 4.9 ESR 12
- UA: 2+ ket, BMP: nl, gluc 92
- Blood and urine cultures sent
- CXR : Neg
- CAT scan of head for worsening headache and "declining mental status"
- Head CT: paranasal sinus disease, no intracranial abnormalities

### **Presentation to Cooper PICU**

- Transferred after 24 hr with persistent fever, emesis and headache
- "Fever, r/o bacteremia, unvaccinated. Meningeal signs now. On ceftriaxone men dose. vanc started. Photophobia, fever, headache, more lethargic.
- Spoke with ID at St. Chris. Rec spinal tap. O2 Sats ok, HR 130's. CT head sinus disease . Fever rectal 38.5. BC negative to date.
- 37.7 today. Febrile this AM. Opens eyes, not vocalizing. Laying in bed, won't walk around. Vomited x4 "

#### Physical Exam on admission to Cooper PICU

VS: Afebrile, VSS

Constitutional: Resting comfortably in bed watching movie Head/Ears/Mouth/Throat: Normal Eyes: PERRLA, EOMI, normal conjunctiva & no discharge

Nose: Nasal discharge present. Neck: +Neck weakness, struggling to hold head up

No cervical adenopathy Cardiovascular: RRR, nl S1 and S2. No murmur Pulmonary/Chest: CTAB, no increased WOB Abdominal: Soft, nontender, nondistended, no HSM Genitourinary: Penis normal. Circumcised. Testes descended BL Musculoskeletal: Normal range of motion Neurological: Alert. Moves all extremities equally, strength 5/5, nl tone Skin: + insect bites on lower extremities

# Cooper PICU Course

- Continued on ceftriaxone and vancomycin
- Nasal wash for viral isolation
- Lyme serology sent
- LP performed:
  <u>CSF Analysis:</u>
  Protein: 48
  Glucose: 57
  RBC: 0

WBC: 194 (80% L; 2% PMN; 18% M) CSF for enterovirus PCR sent Blood and urine cultures from OSH: No growth x 48 hrs Nasal wash viral PCR negative Diagnosed with "viral meningitis" Antibiotics discontinued.

Afebrile Transferred to pediatric floor on HD #2 (Day 5 of illness)

# **Continued Hospital Course**

- Persistent HA, persistent emesis, parents feel child is in pain
- Refusal to walk or bear weight, insists on lying supine; will not straighten legs
- ? Possible post-spinal headache
- 2nd read on head CT: maxillary, ethmoid , sphenoid fullness with air fluid level in maxillary sinus. Diffuse sinus disease but no intracranial abnormality noted
- ID Consulted hospital day #4

## Hospital day # 4: ID Assessment

Extremely uncomfortable, not verbalizing normally, crying , complaining of pain. Most comfortable in fetal position. Refuses to move neck. Will not sit or stand.

- PE: reduced tone of neck muscles, cries with movement, decreased tone of LUE
- Assessment: Abnormal neurologic exam, clinical course not suggestive of viral meningitis
- Recommendation: Pediatric neurology consult, MRI of brain, acyclovir and ceftriaxone, send CSF for HSV

# Pediatric Neurology Consultation

- Nonfocal neuro exam: pt did not sit up or walk
- No clinical evidence for increased ICP, focal deficits or spinal deficits. No signs of encephalopathy
- Rec: Brain MRI to assess for ADEM
- Brain MRV w/o contrast

Work-Up:

- Normal MRI of the brain
- Normal MRV of the brain: no evidence of venous sinus thrombosis
- Normal EEG
- Lyme titer: Neg: ceftriaxone discontinued
- HSV PCR: Neg: acyclovir discontinued

# HD #5-8

- Emesis continued
- Persistent head and neck pain
- New abdominal pain
- Intermittently screaming and thrashing in pain
- Treated with famotidine, ondansetron, caffeine
- CSF enterovirus PCR: Neg

# HD #9

- Neuro exam:
  - Unable to lift L arm > 90°;
     Decreased movement of L leg
- PM&R eval: Prox. motor weakness
  - Decreased L shoulder movement in all planes
  - Decreased L hip flexion
- Head control poor
- Refuses to sit or bear weight
- MRI of the brain and cervical spine ordered



Appears to be **increased signal of the central gray extending** from level of inferior aspect of C3 through superior aspect of C6



The survey sagittal images of the thoracic and lumbar spine demonstrate no definite abnormal signal. However, there is questionable enhancement of ventral nerve roots in the lumbar spine.



On postcontrast imaging, there is the suggestion of **enhancement centrally within the spinal cord,** within the area of abnormal signal identified on precontrast sequences

The above findings can be seen in setting of clinically suspected **acute flaccid myelitis.** Acute transverse myelitis could also have this appearance. This would be an uncharacteristic presentation for acute disseminated encephalomyelitis (ADEM)

# Follow-Up

- Patient transferred to inpatient pediatric rehab on HD #16
- Hospitalized there for 45 day
- October 12<sup>th</sup> November 8<sup>th</sup>
- Condition at D/C:
  - Walking
  - Still has some proximal lower extremity weakness and trunk
  - Mild L upper extremity weakness: functional

#### Acute Flaccid Myelitis (AFM) Overview and Epidemiology

- Acute flaccid myelitis: polio-like illness defined by acute onset of flaccid paralysis with spinal MRI demonstrating a longitudinal lesion in the gray matter of cord.
- Clusters of AFM noted in California and Colorado in 2014, with additional cases across US that year; another spike in cases in 2016.....new peak in 2018.
- Increase in AFM cases in 2014 coincided with national outbreak of severe respiratory illness caused by enterovirus D68.
- Among confirmed AFM cases, CDC has not consistently detected EV-D68: other viruses have been detected (not West Nile).
- Pattern of spinal cord involvement similar to poliomyelitis suggests a viral infection, but definitive connection with a particular virus not yet established
- Late summer and fall predominance! Seasonal clustering every other year



Timeline of clinical features of acute flaccid myelitis cases in the United States 2012– 2015. CMAPs = compound muscle action potentials; CSF = cerebrospinal fluid; EMG = electromyography; GI = gastrointestinal; MUPs = motor unit potentials; NCV = nerve conductionvelocity.





A–D, Acute imaging performed at 2–3 days in patient 1 demonstrates T2 hyperintensity in the right dorsal pons (white arrow, A) and more ill-defined central gray matter hyperintensity seen more commonly in the acute phase (white arrows, B and C; black arrows, D). E–I, Subacute imaging of the spine performed in the same patient at 38 days demonstrates contraction of the cord T2 hyperintensity to focally involve the anterior horn cells (black arrows, E; white arrows, F and H) and nerve root enhancement of ventral cervical roots (*white arrows*, G) and the cauda equina (white arrows, I). Maloney et al. AJNR Am J Neuroradiol 2015:36:245-250

#### **AFM: Clinical Features**

- Presents with an acute onset of asymmetric flaccid paralysis in the setting of a febrile, usually respiratory, illness
- Accompanying sx include headache, neck pain, cranial nerve findings (facial palsy, diplopia, dysphagia), and pain in the affected limbs
- Initial evaluation includes lumbar puncture, MRI with and without contrast of spinal cord, and brain MRI
- CSF findings include: mild pleocytosis with lymphocytic predominance; normal to mildly elevated protein
- AFM may mimic other neurologic disorders such as: Guillain-Barre (GBS)
   Acute disseminated encephalomyelitis (ADEM)
   Transverse myelitis

• Consider ICU Admission in case of:

1. Respiratory muscle weakness as determined by:

- a. Clinical exam
- b. Hypoxia
- c. Hypercarbia
- d. Vital capacity < 15 mL/kg e.
- e. Negative inspiratory force (NIF) < 30 cmH2O
- 2.Impaired airway protection due to:
  - A. Bulbar weakness
  - B. Altered mental status
  - C. Autonomic instability
  - D. Cervical lesion(s) on MRI
  - E. Rapidly progressive course

In the ED: evaluate for other neurologic causes of limb weakness (e.g., HSV neurologic infection, bacterial infections of CNS, GBS syndrome, ADEM)

> Perform a Careful Neurologic Exam!

# Number of confirmed U.S. AFM cases reported to CDC by month of onset, August 2014 - October $2018^{*+}$



Month of onset

## Clinical Features of the 2018 AFM Cases

- Median age: 4 years (range: 7 months–32 yrs), (59%) male, (86%) white
- During 4 weeks preceding onset of limb weakness, signs and symptoms c/w viral illness in 99%
  - fever 65 (81%)
  - respiratory symptoms 62 (78%)
  - gastrointestinal symptoms (38%)
- Upper limb only involvement(47.5%)
- Lower limb only (8.8%)
- 2-3 upper and lower limbs (15.0%)
- All 4 limbs (28.8%)
- All patients with confirmed AFM hospitalized; 59% admitted to ICU
- No deaths reported

FIGURE. Number of confirmed cases of acute flaccid myelitis (AFM) reported to CDC, by month of onset — United States, January–October 2018\*



\* Confirmed AFM cases that CDC was made aware of as of November 2, 2018. Patients under investigation are still being classified, and the case counts are subject to change.

# CSF Findings in 2018 AFM Cases

- Median interval from limb weakness to CSF collection was 1 day
- Median interval from sign or symptom onset to CSF collection:
  - 7 days for respiratory illness
  - 4 days for gastrointestinal symptoms
  - 3 for fever
- Among confirmed cases with available CSF results (98%)
- 83% had pleocytosis
- Median cell count 103 cells/mm<sup>3</sup> (range = 6–814; IQR = 56–194); most with lymphocyte predominance
- Median CSF protein and glucose 47 mg and 59 mg per dL

# Virologic Evaluation by the CDC

- Enterovirus/rhinovirus (EV/RV) testing in all patients meeting clinical criteria for AFM
- Of 80 confirmed cases in 2018, testing performed on 125 clinical specimens from 89% patients, including 21 CSF, 59 upper respiratory, and 45 stool/rectal swab specimens
- 38 (54%) patients + by EV/RV real-time RT-PCR testing, including
  - 11 (29%) for EV-A71,
  - 14 (37%) for EV-D68, and
  - 13 (34%) for other viruses, primarily from nonsterile sites.
- CSF specimens from 2 patients +
  - One CSF + ve for EV-A71; stool specimen also +
  - One CSF + ve for EV-D68; 1 also had EV-D68 and parechovirus-A6 d in a respiratory.
- Multiple viruses detected in respiratory and stool specimens

#### What CDC has learned since 2014

•>90% pts had mild respiratory illness or fever consistent with viral infection before they developed AFM.

•These AFM cases not caused by poliovirus; all stool specimens from AFM patients tested negative for poliovirus.

•Coxsackievirus A16, EV-A71, and EV-D68 in spinal fluid of four of

440 confirmed cases of AFM since 2014, which points to the cause of their AFM

•For all other patients, no pathogen (germ) has been detected in their spinal fluid to confirm a cause

•Most patients had onset of AFM between August and October, with increases in AFM cases every two years since 2014

•Most AFM cases are children (over 90%) and have occurred in 46 states and DC

#### Patient #2

- 3 yr old female, well until 4 days PTA when she began pulling on ear, brought to Cooper Pediatrics office
- Had been cranky and pulling at her R ear x 2 days :fever of 102 night before R TM erythematous, bulging and mild erythema of the tonsils. Amoxicillin Rx.
- On DOA, GM noted child unsteady on her feet, falling repeatedly and then refused to walk and insisted on being carried.
- Taken to outside ED, where she fell off bed : negative head CT.
- $\operatorname{Rx} \Delta$  to augmentin, D/C home but family drove to Cooper ED.
- PE: very fussy ,seems uncomfortable, febrile, extremely unsteady on standing. Evaluated by neurology consultant, underwent LP, admitted to the pediatric floor.
- Because of the concern for acute flaccid myelitis an MRI of the head and spine was performed.

#### Patient's Lab Profile

WBC 10.6 N 43% L 40% M 14%

Hgb 13.5 MCV Plt 284 K

10/19/18	
GLUCOSE	137
BUN	9
CREATININE	0.28
SODIUM	137
POTASSIUM	4.0
CHLORIDE	100
CO2	23
CALCIUM	9.3
ANION GAP	14

CSF APPEARANCE		<u>CLEAR AND</u> COLORLESS
CSF NUCLEATED CELLS	196	<u>187</u>
CSF RBC	<1	<u>23</u>

10/19/18		
SOURCE		CEREBROSPINAL FLUID
ENTEROVIRUS RNA,PCR	NOT DETECTED	NOT DETECTED

CSF Glucose: 70 CSF Protein: 36

# Hospital Course and Rehab Course

- Treated with 2 gram/kg of IVIG over 2 days
- Discharged to pediatric rehab facility on HD #6
- Clinical course to date:
- Admitted since October 24, anticipate another couple of weeks
- Able to sit up, able to roll in bed, still has L lower leg paresis, trace strength back, not able to walk, can get in quadruped position and scoot with 3 extremities
- R upper extremity proximal weakness, functional, use it as an assist, able to feed herself
- Still on Neurontin, stopped Lidoderm patch

**Treatment**: No indication that any specific targeted therapy or intervention should be either preferred or avoided in the treatment of AFM

- Currently no targeted therapies/interventions with enough evidence to endorse or discourage their use for Rx or management of AFM.
- What has been tried:
  - Corticosteroids
  - Intravenous immunoglobulin
  - Plasmapheresis
  - Fluxoetine
  - Antivirals
  - Interferon
  - Other immunosuppressive medications/biological modifiers